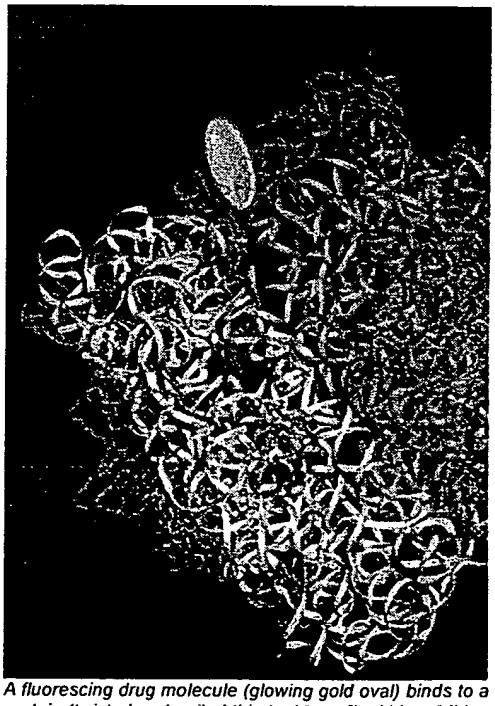
MESA: Measuring Enzyme-Substrate Affinities

The MESA technology, developed in Chemistry Division, has the potential to revolutionize the way the pharmaceutical industry discovers and brings new drugs to market. This amazing technique has won a 2005 R&D 100 Award and is the core technology behind a new Los Alamos spin-off company, Caldera Pharmaceuticals Inc. Caldera will mature the technology and bring it to market.

MESA is a low-cost assay for detecting the binding of drugs to proteins (and other biomolecules and cell structures) without the biasing influence of added fluorescent molecular labels. The assay images drug-protein binding using atoms intrinsic to drug molecules themselves. Because of this label-free detection, MESA captures and quantitates all drug-protein binding, including bindings that are potentially therapeutic and those that are potentially toxic. This allows MESA measurements to generate a complete therapeutic index early in the drug-development process. Today's high drug-development failure rate—the primary cause of the high cost of new drugs—is driven by the inability to measure more than an infinitesimal number of protein-drug interactions. It is estimated that the cost for fully developing a new drug is well over a billion dollars. MESA's ability to measure a very large number of these interactions and its resulting early detection of toxicity could prevent the late stage clinical failures that consume up to 80% of pharmaceutical development costs.



A fluorescing drug molecule (glowing gold oval) binds to a protein (twisted-and-coiled thin teal "rope") within a "ribbon" representation of a bacterial ribosome, a frequent target for antibiotic drugs. This binding of the native drug to protein molecule would be unambiguously detected by MESA label-free measurement technology. The currently standard techniques, which rely on detecting a drug whose structure has been altered by an attached fluorescent label, might not detect the binding.

Applications

- Drug Development: Screens label-free drugs against the proteome in 24–72

hours, compared with extant technologies that test drug effects on less than 0.5% of the body's proteins.

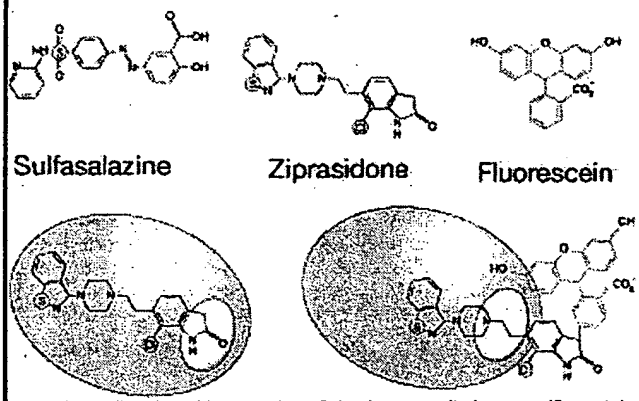
- Personalized Medicine: Allows individual patients to be screened for their likely response to drugs so that the right drug can be prescribed and adverse drug reactions can be reduced.
- Target Validation: Facilitates the identification of new protein targets for drug therapies, a necessity for developing cures for currently intractable or incurable diseases.

Postdoctoral researcher Edel Minogue binds proteins to a slide for analysis.

Benefits

- Fast: Measures drug selectivity for many proteins at throughputs comparable to best-in-class pharmaceutical industry standards for measuring much simpler single drug-protein affinity.
- Reveals therapeutic index: Identifies not only whether a drug will be effective, but also whether it will be safe.
- Inexpensive: Eliminates the need for fluorescent labeling, which consumes both time and money.
- Label-Free Accuracy: Provides far more accurate data than that obtained with fluorescently labeled molecules.

Comparison to state-of-the-art.



Many drugs like ziprasidone work by fitting into a cavity in a specific protein (light-blue spheroid). When drugs are labeled with compounds like fluorescein, they often no longer fit into a protein cavity (fluorescein-labeled ziprasidone, lower right) that would otherwise accommodate them (unlabeled ziprasidone, lower left); this yields false data and, therefore, compromises any data derived from the fluorescently labeled drug. By contrast, MESA uses the intrinsic features of many drugs to measure drug-protein binding.

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